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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/818,939	KARIMOVA ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *96-146* is/are pending in the application.

4a) Of the above claim(s) *108-146* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *96-107* is/are rejected.

7)☒ Claim(s) *101* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0704*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response, on July 26, 2004, to the First Action on the Merits of this case, mailed February 11, 2004, is acknowledged. It is acknowledged that applicants have cancelled Claims 1-95 and added Claims 96-146. Claims 96-146 are pending. Claims 108-146 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Claims 96-107 are hereby considered.

It is acknowledged that the Examiner has required restriction between product and process claims. Where Applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the Official Gazette notice dated March 26, 1996 (1184 O.G. 86; see also M.P.E.P. 821.04, *In re* Ochiai, and *In re* Brouwer). Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right, if the amendment is presented prior to final rejection or allowance, whichever is earlier. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. To be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112.

Claims-Objections

Claim 101 is objected to for improper Markush language. Lines 3 and 9 of Claim 101 should be amended to either "...are selected from the group consisting of: ...138 to 400 of CyaA; and..." or, alternatively, "...are one of either: ...138 to 400 of CyaA; or...".

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Double Patenting

> The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
> A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).
> Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Claims 96-107 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 2-5 and 8 of SN10/240,102. Although the conflicting claims are not identical, Claim 96, Claim 97, Claim 100, Claims 98, 99, and 101-105, and Claims 106 and 107 herein are not patentably distinct from Claim 2, Claim 3, Claim 4, Claim 5, and Claim 8, respectively, of SN10/240,102.

Claim 96 herein and Claim 2 of SN10/240,102 are both directed to an amplification system using chimeric polypeptides comprising fragments derived from an adenylate cyclase.

The claims differ in that Claim 2 of SN10/240,102 also recites an amplification system using chimeric polypeptides derived from guanylate cyclase.

Claim 97 herein and Claim 3 of SN10/240,102 are both directed to an amplification system using chimeric polypeptides comprising fragments derived from the first 400 amino acids of a *Bordetella* adenylate cyclase. The claims differ in that Claim 97 herein also recites an amplification system using chimeric polypeptides derived any region of the adenylate cyclase catalytic domain.

Claims 98, 99, and 101-105 herein and Claim 5 of SN10/240,102 are both directed to an amplification system using chimeric polypeptides comprising the following fragment pairs, which are derived from the first 400 amino acids of *B. pertussis* adenylate cyclase: (a) residues 1-224 and 225-399, (b) residues 1-224 and 224-384, (c) residues 1-137 and 138-400, (d) residues 1-317 and 318-400. The claims differ in that Claim 5 of SN10/240,102 also recites an amplification system using chimeric polypeptides comprising said fragments derived from adenylate cyclases of other species of *Bordetella* as well as any two fragments of an eukaryotic adenylate cyclase in association with a G-protein or forskolin. The claims also differ in that Claims 98 and 99 herein also recite an amplification system using any fragments derived from the first 400 residues of *B. pertussis* adenylate cyclase.

Claim 100 herein and Claim 4 of SN10/240,102 are both directed to an amplification system using chimeric polypeptides comprising fragments derived from a *B. pertussis* adenylate cyclase, wherein the fragments functionally interact with a natural activator *in vitro*. The claims differ in that Claim 4 of SN10/240,102 also recites an amplification system using chimeric polypeptides derived from adenylate cyclases from other species of *Bordetella*.

Claims 106 and 107 herein and Claim 8 of SN10/240,102 are both directed to an amplification system using chimeric polypeptides comprising the following fragment pairs derived from *B. pertussis* adenylate cyclase: (a) residues 1-224 and 225-399, (b) residues 1-224 and 224-384, (c) residues 1-137 and 138-400, (d) residues 1-317 and 318-400, wherein the fragments functionally interact with calmodulin *in vitro*. The claims differ in that Claim 8 of SN10/240,102 also recites an amplification system using chimeric polypeptides derived from (i) any enzyme, (ii) any adenylate cyclase or guanylate cyclase, or (iii) the first 400 residues of any *Bordetella* adenylate cyclase. The claims also differ in that Claim 106 also recites an amplification system using chimeric polypeptides comprising fragments derived from the first 400 amino acids of *B. pertussis* adenylate cyclase.

The portion of the specification in SN10/240,102 that supports the recited amplification systems therein includes embodiments that would anticipate Claims 96-107 herein, e.g., the specific amplification systems, as described above, which are the same systems encompassed by Claims 2-5 and 8 of SN10/240,102. Claims 96-107 herein cannot be considered patentably distinct over Claims 2-5 and 8 of SN10/240,102 when there are specifically recited embodiments (the amplification systems described above) that would anticipate Claims 98-107 herein. Alternatively, Claims 98-107 herein cannot be considered patentably distinct over Claims 2-5 and 8 of SN10/240,102 when there are specifically disclosed embodiments in SN10/240,102 that supports Claims 2-5 and 8 of that Application and falls within the scope of Claims 98-107 herein, because it would have been obvious to a skilled artisan to modify the amplification systems of Claims 2-5 and 8 of SN10/240,102 by selecting a specifically disclosed embodiment that supports those claims, as disclosed in SN10/240,102. One having ordinary skill in the art

would have been motivated to do this, because such embodiments are disclosed as being preferred embodiments for Claims 2-5 and 8 of SN10/240,102.

This is a provisional obviousness-type double patenting rejection. because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 99-105 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 99 recites: "...wherein the first and second fragments are complementary". Neither the claims nor the specification define "complementary". The specification states: "The catalytic domain can be proteolytically cleaved into two complementary fragments, T25 and T18, that remain associated in the presence of CaM in a fully active ternary complex" (pg 24, lines 8-10). Based on said statement, Claim 99 has three possible interpretations. Does Applicant mean to recite that the first and second fragments (a) are structural complements produced from a single cleavage of the catalytic domain and together make up the complete structure of the catalytic domain, (b) are structural complements and, therefore, associate/bind each other, or (c) are functional complements, which together reconstitute the activity of the catalytic domain? Because the meaning of the phrase "complementary" is unclear, Claim 99 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite.

Claim 100 recites: "...a natural activator of the *Bordetella pertussis* adenylate cyclases...". The specification states: "The natural activator can be the calmodulin (CaM), or a fragment thereof...". A person of ordinary skill in the art would not know the metes and bounds of the recited "natural activator". Although the specification states that the activator can be calmodulin, it does not disclose whether or not the activator can be anything other than calmodulin. The specification also states: "The fragment of calmodulin can be about 70 amino acids long, corresponding preferentially, to residues 77 to 148 of mammalian calmodulin, as described in WO 99/28746". The phrase "preferentially" renders the definition of the scope of the calmodulin fragments indefinite, because it is unclear what fragments, other than residues 77-148, are encompassed by the definition of "a natural activator". Furthermore, it is unlikely that a fragment of calmodulin is a "natural activator", as defined to be a compound that activates calmodulin within a cell. Because a skilled artisan would not know the metes and bounds of the invention, Claim 100 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Claims 101-105, as dependent on Claim 100, are rejected under 35 U.S.C. 112, second paragraph, for the same reasons.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

In this regard, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These

factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include, but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; and (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Rejection of Claims 50-56 and 94 under 35 U.S.C. 112, first paragraph, because the application did not satisfy the enablement requirements regarding the public availability of the novel cells, BTH101 and DHM, is rendered moot by cancellation of said claims. However, for the same reasons, Claims 96-107 are hereby rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The deposit declaration of Danielle Berneman is acknowledged. However, neither said declaration nor the response of July 26, 2004 by Applicant's representative, Kenneth Meyers, make the following statement: "that the cells will be irrevocably and without restriction or condition be released to the public upon the issuance of the patent". As described in the prior action, said statement is necessary to fulfill the enablement requirements of 35 U.S.C. § 112. Therefore, Claims 96-107 are rejected under 35 U.S.C. § 112, first paragraph.

The further rejection of Claims 50-52, 54-56, and 94 under 35 U.S.C. 112, first paragraph, for lack of enablement, is also rendered moot by cancellation of said claims. However, Claim 96 is herein rejected under 35 U.S.C. 112, first paragraph, for lack of enablement for the same reasons described in the prior action. In support of their request for withdrawal of the rejection of Claims 50-52, 54-56, and 94 under 35 U.S.C. 112, first paragraph, Applicants provide the following arguments, which are relevant to rejection of Claim 96 herein. First, Applicants provide a statement of the Wands factors and a restatement of the claims. Applicants argue the following. (1) That, adenylate cyclases enzymes and their structures as well as fragments of adenylate cyclases that can be used to reconstitute activity were well known in the art as of the filing date of the instant application (Applicants cite Tang et al, 1995 and Tesmer et al, 1997). (2) That it was predictable that recombining fragments of catalytic domains from an adenylate cyclase enzyme would form an active catalytic domain. (3) That, the working example, which uses the T25 and T18 fragments of the *B. pertussis* adenylate cyclase, demonstrates convincingly that the amplification system works when fragments of a catalytic domain of an adenylate cyclase enzyme are used. (4) That, the Office has not provided any reason why one of skill in the art would not consider Applicants' teaching and statement as applying to the full breadth of the invention as claimed.

These arguments are not found to be persuasive for the following reasons.

(1) It is acknowledged that Tesmer et al teach the crystal structures of some known and chimeric adenylate cyclases and that Tang et al teach construction of a soluble, chimeric adenylate cyclase. However, adenylate cyclases are a large family of enzymes encoded by at least nine different genes, with additional variants arising from alternative splicing (Krupinski

and Cali, 1998; pg 53, parg 2). Homology between members of this family ranges from 69% identity, between adenylate cyclase Type V and Type VI, to as low as 34% identity, for Type IV with any other type (*Ibid*; pg 55, parg 1). Claim 96 recites an amplification system derived from any protein with adenylate cyclase activity. The scope of proteins encompassed includes any of an extremely large number of variants derived from known adenylate cyclases and well as any previously unidentified proteins having any structure and having adenylate cyclase activity. Clearly it would be an undue burden to make and test all chimeric polypeptides comprising any fragment derived from any protein encompassed by said scope.

(2) It is acknowledged that chimeras derived from a known active adenylate cyclase polypeptide (such as the *B. pertussis* polypeptide derived from the *cyaA* gene), wherein the chimeras together comprise the complete catalytic domain of the enzyme, are likely to be successful in the recited amplification system. However, as discussed in (1), the scope of Claim 96 is not limited to known, naturally occurring adenylate cyclases. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in an adenylate cyclase's amino acid sequence and which fragments thereof can be used successfully requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to chimeric proteins derived from the *B. pertussis* adenylate cyclase catalytic domain.

(3) See (1) and (2).

(4) Claim 96 fails to provide any structural information regarding the extremely large number of proteins having adenylate cyclase activity or the extremely large number of fragments thereof to be used in the chimeras of the recited amplification system. A person of ordinary skill in the art would predict that, most fragments of any protein having adenylate cyclase activity will not be successful in said system. Without guidance, as described in (2), one would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation.

Written Description

Rejection of Claims 50-52, 54-56, and 94 under 35 U.S.C. 112, first paragraph, for insufficient written description, is rendered moot by cancellation of said claims. Claim 96 is herein rejected under 35 U.S.C. 112, first paragraph, due to insufficient written description, for the same reasons described in the prior action. In support of their request for withdrawal of the rejection of Claims 50-52, 54-56, and 94, Applicants provide the following arguments, which are relevant to rejection of Claim 96 herein. First, Applicants quote the *Regents of the University of California v. Eli Lilly & Co.*: the written description requirement can be met "by disclosure of relevant, identifying characteristics, i.e., such as structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus". Applicants argue that the instant specification meets this standard in its support of the new claims reciting "an adenylate cyclase catalytic domain". Specifically, Applicants quote from the specification: "according to one embodiment of the invention, the enzyme can be selected from the group consisting of adenylate

cyclase and guanylate cyclase from any origin". Applicants argue that said statement, coupled with the knowledge of the art regarding the structure of the catalytic domains of known adenylate cyclases, demonstrates that Applicants were in possession of the full breadth of the claimed invention.

This argument is not found to be persuasive. The scope of Claim 96 encompasses a genus of amplification systems using any two chimeric polypeptides comprising any fragments derived from a catalytic domain of any protein having any structure and having adenylate cyclase activity. Said scope includes polypeptides derived from any of an extremely large number of variants of known adenylate cyclases and well as any previously unidentified proteins having any structure and having adenylate cyclase activity. The specification teaches the structure of only four representative species of such amplifications systems comprising pairs of chimeric polypeptides comprising fragments derived from a single adenylate cyclase catalytic domain. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being two chimeric polypeptides derived from a catalytic domain of any protein having adenylate cyclase activity. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan Lee Swope, Ph.D.

REBECCA E. PRUITY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600